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(21) International Application Number: PCT/US96/11368 (22) International Filing Date: 8 July 1996 (08.07.96) (30) Priority Data: 60/001,452                      17 July 1995 (17.07.95)                      US (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BRIGGS, Christopher, A. [US/US]; 643 East 12th Street, Holland, MI 49423 (US). JENNINGS, Rex, Allen [US/US]; 405 Lincoln Avenue, Holland, MI 49423 (US). WADE, Robert, A. [US/US]; 3882 62nd Street, Holland, MI 49423 (US). HARASAWA, Kikuko [JP/JP]; 202 Liberty Palace Odakyusagami-hara, 18-15, Minamidai 6-chome, Sagami-hara-shi, Kanagawa 228 (JP). ICHIKAWA, Shigeru [JP/JP]; D-403 CI-Heights, 1356 Yamasaki-cho, Machida-shi, Tokyo 195 (JP). MINOHARA, Kazuo [JP/JP]; 702 Park-Heights Sagami-hara, 4-4, Sagami-hara 5-chome, Sagami-hara-shi, Kanagawa 229 (JP). NAKAGAWA, Shinsuke [JP/JP]; 303 Seishin-Hills, 14-30, Seishin 7-chome, Sagami-hara-shi, Kanagawa 229 (JP).		(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.  (81) Designated States: AU, BG, BR, CA, CN, CZ, EE, GE, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, UA, US, UZ, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  Published With international search report.
(54) Title: CRYSTALLINE [R-(R*,R*)]-2-(4-FLUOROPHENYL)-BETA,DELTA-DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID HEMI CALCIUM SALT (ATORVASTATIN)		
(57) Abstract  Novel crystalline forms of [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt designated Form I, Form II, and Form IV are characterized by their X-ray powder diffraction and/or solid state NMR are described, as well as methods for the preparation and pharmaceutical composition of the same, which are useful as agents for treating hyperlipidemia and hypercholesterolemia.		

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- 1 -

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CRYSTALLINE [R-(R\*,R\*)]-2-(4-FLUOROPHENYL)-BETA,DELTA-DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID HEMI CALCIUM SALT (ATORVASTATIN)

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## BACKGROUND OF THE INVENTION

The present invention relates to novel crystalline forms of atorvastatin which is known by the chemical name [R-(R\*,R\*)]-2-(4-fluorophenyl)- $\beta,\delta$ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt useful as pharmaceutical agents, to methods for their production and isolation, to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment. The novel crystalline compounds of the present invention are useful as inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) and are thus useful hypolipidemic and hypocholesterolemic agents.

United States Patent Number 4,681,893, which is herein incorporated by reference, discloses certain trans-6-[2-(3- or 4-carboxamido-substituted-pyrrol-1-yl)alkyl]-4-hydroxy-pyran-2-ones including trans ( $\pm$ )-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

United States Patent Number 5,273,995, which is herein incorporated by reference, discloses the enantiomer having the R form of the ring-opened acid of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, i.e., [R-(R\*,R\*)]-2-(4-fluorophenyl)- $\beta,\delta$ -dihydroxy-5-(1-

-2-

methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid.

United States Patent Numbers 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,280,126; 5,397,792; and 5,342,952, which are herein incorporated by reference, disclose various processes and key intermediates for preparing atorvastatin.

Atorvastatin is prepared as its calcium salt, i.e., [R-(R\*,R\*)]-2-(4-fluorophenyl)- $\beta,\delta$ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). The calcium salt is desirable since it enables atorvastatin to be conveniently formulated in, for example, tablets, capsules, lozenges, powders, and the like for oral administration. Additionally, there is a need to produce atorvastatin in a pure and crystalline form to enable formulations to meet exacting pharmaceutical requirements and specifications.

Furthermore, the process by which atorvastatin is produced needs to be one which is amenable to large-scale production. Additionally, it is desirable that the product should be in a form that is readily filterable and easily dried. Finally, it is economically desirable that the product be stable for extended periods of time without the need for specialized storage conditions.

The processes in the above United States Patents disclose amorphous atorvastatin which has unsuitable filtration and drying characteristics for large-scale production and must be protected from heat, light, oxygen, and moisture.

We have now surprisingly and unexpectedly found that atorvastatin can be prepared in crystalline form. Thus, the present invention provides atorvastatin in new crystalline forms designated Form I, Form II, and

-3-

Form IV. Form I atorvastatin consists of smaller particles and a more uniform size distribution than the previous amorphous product and exhibits more favorable filtration and drying characteristics. Additionally, Form I atorvastatin is purer and more stable than the amorphous product.

## SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to crystalline Form I atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the  $2\theta$ , d-spacings, and relative intensities with a relative intensity of >20% measured after 2 minutes of grinding and measured on a Siemens D-500 diffractometer with  $\text{CuK}\alpha$  radiation:

-4-

	2 $\theta$	d	Relative Intensity (>20%) Ground 2 Minutes
	9.150	9.6565	42.60
	9.470	9.3311	41.94
	10.266	8.6098	55.67
5	10.560	8.3705	29.33
	11.853	7.4601	41.74
	12.195	7.2518	24.62
	17.075	5.1887	60.12
	19.485	4.5520	73.59
10	21.626	4.1059	100.00
	21.960	4.0442	49.44
	22.748	3.9059	45.85
	23.335	3.8088	44.72
	23.734	3.7457	63.04
15	24.438	3.6394	21.10
	28.915	3.0853	23.42
	29.234	3.0524	23.36

20 Further, the present invention is directed to  
 crystalline Form I atorvastatin and hydrates thereof  
 characterized by the following solid-state  $^{13}\text{C}$  nuclear  
 magnetic resonance spectrum wherein chemical shift is  
 expressed in parts per million measured on a Bruker  
 25 AX-250 spectrometer:

- 5 -

		Assignment (7 kHz)	Chemical Shift
		C12 or C25	182.8
		C12 or C25	178.4
5		C16	166.7 (broad) and 159.3
		Aromatic Carbons	
		C2-C5, C13-C18, C19-C24, C27-C32	137.0
			134.9
			131.1
10			129.5
			127.6
			123.5
			120.9
			118.2
15			113.8
		C8, C10	73.1
			70.5
			68.1
			64.9
		Methylene Carbons	
20		C6, C7, C9, C11	47.4
			41.9
			40.2
		C33	26.4
25			25.2
		C34	21.3

In a preferred embodiment of the first aspect of the invention, crystalline Form I atorvastatin is a trihydrate.

In a second aspect, the present invention is directed to crystalline Form II atorvastatin and hydrates thereof characterized by the following X-ray

-6-

powder diffraction pattern expressed in terms of the  $2\theta$ , d-spacings, and relative intensities with a relative intensity of >20% measured after 2 minutes of grinding and measured on a Siemens D-500 diffractometer with  $\text{CuK}\alpha$  radiation:

	$2\theta$	d	Relative Intensity (>20%) Ground 2 Minutes
	5.582	15.8180	42.00
	7.384	11.9620	38.63
10	8.533	10.3534	100.00
	9.040	9.7741	92.06
	12.440 (broad)	7.1094	30.69
	15.771 (broad)	5.6146	38.78
	17.120-17.360 (broad)	5.1750-5.1040	63.66-55.11
15	19.490	4.5507	56.64
	20.502	4.3283	67.20
	22.706-23.159 (broad)	3.9129-3.8375	49.20-48.00
	25.697 (broad)	3.4639	38.93
	29.504	3.0250	37.86
20			

Further, the second aspect of the present invention is directed to crystalline Form II atorvastatin and hydrates thereof characterized by the following solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million measured on a Bruker AX-250 spectrometer:



- 7 -

	Assignment	Chemical Shift
	Spinning Side Band	209.1
	Spinning Side Band	206.8
	C12 or C25	181 (broad)
5	C12 or C25	163 (broad)
	C16	161 (broad)
	Aromatic Carbons	
	C2-C5, C13-C18, C19-C24, C27-C32	140.5
		134.8
10		133.3
		129.0
		122.9
		121.4
		120.3
15		119.0
		117.1
		115.7
		114.7
	C8, C10	70.6
20		69.0
		68.0
		67.3
	Spinning Side Band	49.4
	Spinning Side Band	48.9
25	Methylene Carbons	
	C6, C7, C9, C11	43.4
		42.3
		41.7
		40.2
30	C33	27.5
	C34	22.8 (broad)

-8-

In a third aspect, the present invention is directed to crystalline Form IV atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the  $2\theta$ , d-spacings, and relative intensities with a relative intensity of >15% measured on a Siemens D-500 diffractometer with  $\text{CuK}\alpha$  radiation:

	$2\theta$	d	Relative Intensity (>15%)
10	4.889	18.605	38.45
	5.424	16.2804	20.12
	5.940	14.8660	17.29
	7.997	11.0465	100.00
	9.680	9.1295	67.31
15	10.416	8.4859	20.00
	12.355	7.1584	19.15
	17.662	5.0175	18.57
	18.367	4.8265	23.50
	19.200	4.6189	18.14
20	19.569	4.5327	54.79
	21.723	4.0879	17.99
	23.021	3.8602	28.89
	23.651	3.7587	33.39
	24.143	3.6832	17.23

25

Further, the fourth aspect of the present invention is directed to Form IV atorvastatin and hydrates thereof characterized by the following solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum wherein chemical shift is expressed as parts per million measured on a Bruker AX-250 spectrometer:

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- 9 -

	Assignment	Chemical Shift
	C12 or C25	186.4
		184.9
	C12 or C25	181.4
		179.3
	C16	166.1 (broad)
		and
		159.0 (broad)
5	Aromatic Carbons	
	C2-C5, C13-C18, C19-C24, C27-C32	138.1 (broad)
		134.7
		129.2
		127.1
		122.7
		119.8
		115.7
10	C8, C10	71.5
		67.9
		66.3
		63.5
	Methylene Carbons	
	C6, C7, C9, C11	46.1
		43.4
		42.1
		40.0
	C33	25.9
	C34	20.3
		19.4
		17.9
15		

-10-

As inhibitors of HMG-CoA, the novel crystalline forms of atorvastatin are useful hypolipidemic and hypocholesterolemic agents.

5 A still further embodiment of the present invention is a pharmaceutical composition for administering an effective amount of crystalline Form I, Form II, or Form IV atorvastatin in unit dosage form in the treatment methods mentioned above. Finally, the present invention is directed to methods  
10 for production of Form I, Form II, or Form IV atorvastatin.

#### BRIEF DESCRIPTION OF THE DRAWINGS

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The invention is further described by the following nonlimiting examples which refer to the accompanying Figures 1 to 6, short particulars of which are given below.

20

##### Figure 1

Diffractionogram of Form I atorvastatin ground for 2 minutes (Y-axis = 0 to maximum intensity of 3767.50 counts per second (cps))

25

##### Figure 2

Diffractionogram of Form II atorvastatin ground for 2 minutes (Y-axis = 0 to maximum intensity of 1500 cps)

30

##### Figure 3

Diffractionogram of Form IV atorvastatin (Y-axis = 0 to maximum intensity of 8212.5 cps).

-11-

Figure 4

Solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum with spinning side bands identified by an asterisk of Form I atorvastatin.

5

Figure 5

Solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum with spinning side bands identified by an asterisk of Form II atorvastatin.

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Figure 6

Solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum with spinning side bands identified by an asterisk of Form IV atorvastatin.

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## DETAILED DESCRIPTION OF THE INVENTION

Crystalline Form I, Form II, or Form IV atorvastatin may be characterized by their X-ray powder diffraction patterns and/or by their solid state nuclear magnetic resonance spectra (NMR).

20

## X-RAY POWDER DIFFRACTION

25

Forms I, II, and IV Atorvastatin

Forms I, II, or Form IV atorvastatin were characterized by their X-ray powder diffraction pattern. Thus, the X-ray diffraction patterns of Forms I, II, and Form IV atorvastatin were measured on a Siemens D-500 diffractometer with  $\text{CuK}_\alpha$  radiation.

30

Equipment

Siemens D-500 Diffractometer-Kristalloflex with an IBM-compatible interface, software = DIFFRAC AT (SOCABIM 1986, 1992).

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-12-

CuK<sub>a</sub> radiation (20 mA, 40 kV,  $\lambda = 1.5406 \text{ \AA}$ ) slits I and II at 1°) electronically filtered by the Kevex Psi Peltier Cooled Silicon [Si(Li)] Detector (Slits: III at 1° and IV at 0.15°).

5

#### Methodology

The silicon standard is run each day to check the X-ray tube alignment.

Continuous  $\theta/2\theta$  coupled scan: 4.00° to 40.00° in  $2\theta$ , scan rate of 6°/min: 0.4 sec/0.04° step.

10

Sample tapped out of vial and pressed onto zero-background quartz in aluminum holder. Sample width 13-15 mm.

Samples are stored and run at room temperature.

15

#### Grinding/Sieving

Grinding is used to minimize intensity variations for the diffractogram disclosed herein. However, if grinding significantly altered the diffractogram or increased the amorphous content of the sample, then the diffractogram of the unground sample was used. Grinding was done in a small agate mortar and pestle. The mortar was held during the grinding and light pressure was applied to the pestle.

20

25

Ground Form II atorvastatin was sieved through a 230 mesh screen before analysis by x-ray diffraction.

30

Table 1 lists the  $2\theta$ , d-spacings, and relative intensities of all lines in the unground sample with a relative intensity of >20% for crystalline Form I atorvastatin. Table 1 also lists the relative intensities of the same lines in a diffractogram measured after 2 minutes of grinding. The intensities of the sample ground for 2 minutes are more

35

-13-

representative of the diffraction pattern without preferred orientation. It should also be noted that the computer-generated, unrounded numbers are listed in this table.

5

TABLE 1. Intensities and Peak Locations of all Diffraction Lines With Relative Intensity Greater Than 20% for Form I Atorvastatin

	2 $\theta$	d	Relative Intensity (>20%) No Grinding	Relative Intensity (>20%)* Ground 2 Minutes
10	9.150	9.6565	37.42	42.60
	9.470	9.3311	46.81	41.94
	10.266	8.6098	75.61	55.67
	10.560	8.3705	24.03	29.33
15	11.853	7.4601	55.16	41.74
	12.195	7.2518	20.03	24.62
	17.075	5.1887	25.95	60.12
	19.485	4.5520	89.93	73.59
	21.626	4.1059	100.00	100.00
20	21.960	4.0442	58.64	49.44
	22.748	3.9059	36.95	45.85
	23.335	3.8088	31.76	44.72
	23.734	3.7457	87.55	63.04
	24.438	3.6394	23.14	21.10
25	28.915	3.0853	21.59	23.42
	29.234	3.0524	20.45	23.36

\* The second relative intensity column gives the relative intensities of the diffraction lines on the original diffractogram after 2 minutes of grinding.

30

Table 2 lists the 2 $\theta$ , d-spacings, and relative intensities of all lines in the ground/sieved sample

-14-

with a relative intensity of >20% for crystalline Form II atorvastatin. It should also be noted that the computer-generated unrounded numbers are listed in this table.

5

TABLE 2. Intensities and Peak Locations of All Diffraction Lines With Relative Intensity Greater Than 20% for Form II Atorvastatin

	2 $\theta$	d	Relative Intensity (>20%)
10	5.582	15.8180	42.00
	7.384	11.9620	38.63
	8.533	10.3534	100.00
	9.040	9.7741	92.06
15	12.440 (broad)	7.1094	30.69
	15.771 (broad)	5.6146	38.78
	17.120-17.360 (broad)	5.1750-5.1040	63.66-55.11
	19.490	4.5507	56.64
	20.502	4.3283	67.20
20	22.706-23.159 (broad)	3.9129-3.8375	49.20-48.00
	25.697 (broad)	3.4639	38.93
	29.504	3.0250	37.86

25 Table 3 lists the 2 $\theta$ , d-spacings, and relative intensities of all lines in the unground sample with a relative intensity of >15% for crystalline Form IV atorvastatin. It should also be noted that the computer-generated unrounded numbers are listed in this

30 table.



-15-

TABLE 3. Intensities and Peak Locations of All  
Diffraction Lines With Relative Intensity  
Greater Than 15% for Form IV Atorvastatin

	$2\theta$	d	Relative Intensity (>15%)
5	4.889	18.605	38.45
	5.424	16.2804	20.12
	5.940	14.8660	17.29
	7.997	11.0465	100.00
	9.680	9.1295	67.31
10	10.416	8.4859	20.00
	12.355	7.1584	19.15
	17.662	5.0175	18.57
	18.367	4.8265	23.50
	19.200	4.6189	18.14
15	19.569	4.5327	54.79
	21.723	4.0879	17.99
	23.021	3.8602	28.89
	23.651	3.7587	33.39
	24.143	3.6832	17.23
20			

# SOLID STATE NUCLEAR MAGNETIC RESONANCE (NMR)

## 25 Methodology

All solid-state  $^{13}\text{C}$  NMR measurements were made with a Bruker AX-250, 250 MHz NMR spectrometer. High resolution spectra were obtained using high-power proton decoupling and cross-polarization (CP) with magic-angle spinning (MAS) at approximately 5 kHz. The magic-angle was adjusted using the Br signal of KBr by detecting the side bands as described by Frye and Maciel (Frye J.S. and Maciel G.E., J. Mag. Res., 30

-16-

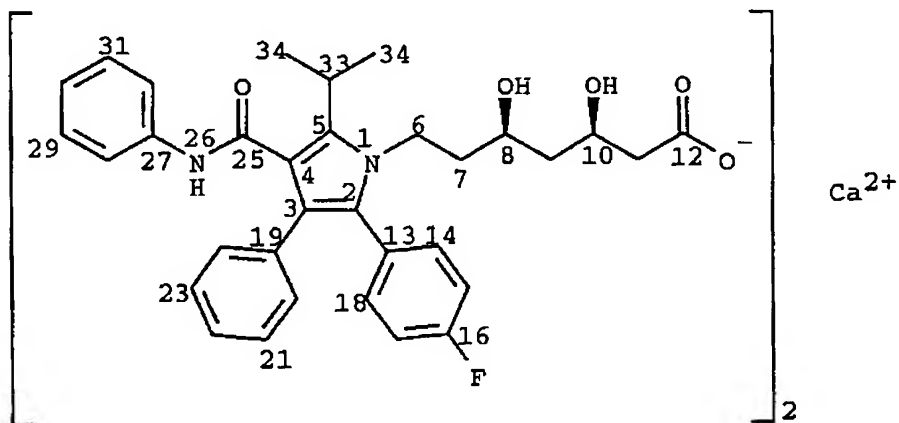
1982;48:125). Approximately 300 to 450 mg of sample packed into a canister-design rotor was used for each experiment. Chemical shifts were referenced to external tetrakis (trimethylsilyl)silane (methyl signal at 3.50 ppm) (Muntean J.V. and Stock L.M., J. Mag. Res., 1988;76:54).

Table 4 shows the solid-state NMR spectrum for crystalline Form I atorvastatin.

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-17-

TABLE 4. Carbon Atom Assignment and Chemical Shift for Form I Atorvastatin

5	Assignment (7 kHz)	Chemical Shift
	C12 or C25	182.8
	C12 or C25	178.4
	C16	166.7 (broad) and 159.3
	Aromatic Carbons	
	C2-C5, C13-C18, C19-C24, C27-C32	137.0
10		134.9
		131.1
		129.5
		127.6
		123.5
15		120.9
		118.2
		113.8
	C8,C10	73.1
		70.5
20		68.1
		64.9
	Methylene Carbons	
	C6, C7, C9, C11	47.4
		41.9
25		40.2
	C33	26.4
		25.2
	C34	21.3

30

Table 5 shows the solid-state NMR spectrum for crystalline Form II atorvastatin.

-18-

TABLE 5. Carbon Atom Assignment and Chemical Shift for Form II Atorvastatin

	Assignment	Chemical Shift
	Spinning Side Band	209.1
5	Spinning Side Band	206.8
	C12 or C25	181 (broad)
	C12 or C25	163 (broad)
	C16	161 (broad)
	Aromatic Carbons	
10	C2-C5, C13-C18, C19-C24, C27-C32	140.5
		134.8
		133.3
		129.0
		122.9
15		121.4
		120.3
		119.0
		117.1
		115.7
20		114.7
		70.6
		69.0
	C8, C10	68.0
		67.3
25	Spinning Side Band	49.4
	Spinning Side Band	48.9
	Methylene Carbons	
	C6, C7, C9, C11	43.4
		42.3
30		41.7
		40.2
	C33	27.5
	C34	22.8 (broad)

-19-

Table 6 shows the solid-state NMR spectrum for crystalline Form IV atorvastatin.

5	TABLE 6. Carbon Atom Assignment and Chemical Shift for Form IV Atorvastatin	
	Assignment	Chemical Shift
	C12 or C25	186.4
		184.9
	C12 or C25	181.4
		179.3
	C16	166.1 (broad) and 159.0 (broad)
10	Aromatic Carbons	
	C2-C5, C13-C18, C19-C24, C27-C32	138.1 (broad)
		134.7
		129.2
		127.1
		122.7
		119.8
		115.7
15	C8, C10	71.5
		67.9
		66.3
		63.5
	Methylene Carbons	
	C6, C7, C9, C11	46.1
		43.4
		42.1
		40.0
	C33	25.9
	C34	20.3
		19.4
		17.9
20		

-20-

Crystalline Form I, Form II, and Form IV atorvastatin of the present invention may exist in anhydrous forms as well as hydrated forms. In general, the hydrated forms, are equivalent to unhydrated forms and are intended to be encompassed within the scope of the present invention. Crystalline Form I atorvastatin contains about 1 to 8 mol of water. Preferably, Form I atorvastatin contains 3 mol of water.

The present invention provides a process for the preparation of crystalline Form I atorvastatin which comprises crystallizing atorvastatin from a solution in solvents under conditions which yield crystalline Form I atorvastatin.

The precise conditions under which crystalline Form I atorvastatin is formed may be empirically determined and it is only possible to give a number of methods which have been found to be suitable in practice.

Thus, for example, crystalline Form I atorvastatin may be prepared by crystallization under controlled conditions. In particular, it can be prepared either from an aqueous solution of the corresponding basic salt such as, an alkali metal salt, for example, lithium, potassium, sodium, and the like; ammonia or an amine salt; preferably, the sodium salt by addition of a calcium salt, such as, for example, calcium acetate and the like, or by suspending amorphous atorvastatin in water. In general, the use of a hydroxylic co-solvent such as, for example, a lower alkanol, for example methanol and the like, is preferred.

When the starting material for the preparation of the desired crystalline Form I atorvastatin is a solution of the corresponding sodium salt, one preferred preparation involves treating a solution of the sodium salt in water containing not less than about 5% v/v methanol, preferably about 5% to 33% v/v

-21-

methanol, particularly preferred about 10% to 15% v/v methanol, with an aqueous solution of calcium acetate, preferably at an elevated temperature at up to about 70°C such as, for example, about 45-60°C, particularly preferred about 47-52°C. It is preferable to use calcium acetate and, in general, 1 mole of calcium acetate to 2 moles of the sodium salt of atorvastatin. Under these conditions, calcium salt formation as well as crystallization should preferably be carried out at an elevated temperature, for example within the above-mentioned temperature ranges. It has been found that it may be advantageous to include in the starting solution a small amount of methyl tert-butyl ether (MTBE) such as, for example, about 7% w/w. It has frequently been found desirable to add "seeds" of crystalline Form I atorvastatin to the crystallization solution in order to consistently produce crystalline Form I atorvastatin.

When the starting material is amorphous atorvastatin or a combination of amorphous and crystalline Form I Atorvastatin, the desired crystalline Form I atorvastatin may be obtained by suspending the solid in water containing up to about 40% v/v, such as, for example, about 0% to 20% v/v, particularly preferred about 5% to 15% v/v co-solvent such as, for example, methanol, ethanol, 2-propanol, acetone, and the like until conversion to the required form is complete, followed by filtration. It has frequently been found desirable to add "seeds" of crystalline Form I atorvastatin to the suspension in order to ensure complete conversion to crystalline Form I atorvastatin. Alternatively, a water-wet cake consisting principally of amorphous atorvastatin can be heated at elevated temperatures such as, for example, up to about 75°C, particularly preferred about 65-70°C, until a significant amount of crystalline Form I

-22-

atorvastatin is present, whereupon the amorphous/  
crystalline Form I mixture can be slurried as described  
above.

5 Crystalline Form I atorvastatin is significantly  
easier to isolate than amorphous atorvastatin and can  
be filtered from the crystallization medium after  
cooling, and washed and dried. For example, filtration  
of a 50 mL slurry of crystalline Form I atorvastatin  
was complete within 10 seconds. A similarly sized  
10 sample of amorphous atorvastatin took more than an hour  
to filter.

The present invention also provides a process for  
the preparation of crystalline Form II atorvastatin  
which comprises suspending atorvastatin in solvents  
15 under conditions which yield crystalline Form II  
atorvastatin.

The precise conditions under which Form II of  
crystalline atorvastatin is formed may be empirically  
determined and it is only possible to give a method  
20 which has been found to be suitable in practice.

Thus, for example, when the starting material is  
amorphous, a combination of amorphous and Form I, or  
crystalline Form I atorvastatin, the desired Form II of  
crystalline atorvastatin may be obtained by suspending  
25 the solid in methanol containing about 40% to about 50%  
water until conversion to the required form is  
complete, followed by filtration.

The present invention also provides a process for  
the preparation of crystalline Form IV atorvastatin  
30 which comprises crystallizing atorvastatin from a  
solution thereof in solvents under conditions which  
yield crystalline Form IV atorvastatin.

The precise conditions under which Form IV of  
crystalline atorvastatin is formed may be empirically  
35 determined and it is only possible to give a method  
which has been found to be suitable in practice.



-23-

Thus, for example, when the starting material is Form I of crystalline atorvastatin, the desired Form IV of crystalline atorvastatin may be obtained by dissolving the solid in methanol whereupon crystalline Form IV precipitates.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either compounds or a corresponding pharmaceutically acceptable salt of a compound of the present invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in

-24-

suitable proportions and compacted in the shape and size desired.

5       The powders and tablets preferably contain from two or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is  
10       intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly,  
15       cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

20       For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

25       Liquid form preparations include solutions, suspensions, retention enemas, and emulsions, for example water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol  
30       solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

35       Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component

-25-

in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

5           Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition  
10           to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

          The pharmaceutical preparation is preferably in  
15           unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as  
20           packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

          The quantity of active component in a unit dose  
25           preparation may be varied or adjusted from 0.5 mg to 100 mg, preferably 2.5 mg to 80 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

30           In therapeutic use as hypolipidemic and/or hypocholesterolemic agents, the crystalline Forms I, II, and Form IV atorvastatin utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 2.5 mg to  
35           about 80 mg daily. A daily dose range of about 2.5 mg to about 20 mg is preferred. The dosages, however, may

-26-

be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

15

## EXAMPLE 1

[R-(R\*,R\*)1-2-(4-Fluorophenyl)- $\beta$ , $\delta$ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form I Atorvastatin)]  
Method A

A mixture of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (atorvastatin lactone) (United States Patent Number 5,273,995) (75 kg), methyl tertiary-butyl ether (MTBE) (308 kg), methanol (190 L) is reacted with an aqueous solution of sodium hydroxide (5.72 kg in 950 L) at 48-58°C for 40 to 60 minutes to form the ring-opened sodium salt. After cooling to 25-35°C, the organic layer is discarded, and the aqueous layer is again extracted with MTBE (230 kg). The organic layer is discarded, and the MTBE saturated aqueous solution of the sodium salt is heated to 47-52°C. To this solution is added a solution of calcium acetate hemihydrate (11.94 kg) dissolved in water (410 L), over at least

-27-

30 minutes. The mixture is seeded with a slurry of crystalline Form I atorvastatin (1.1 kg in 11 L water and 5 L methanol) shortly after addition of the calcium acetate solution. The mixture is then heated to  
5 51-57°C for at least 10 minutes and then cooled to 15-40°C. The mixture is filtered, washed with a solution of water (300 L) and methanol (150 L) followed by water (450 L). The solid is dried at 60-70°C under vacuum for 3 to 4 days to give crystalline Form I  
10 atorvastatin (72.2 kg).

#### Method B

Amorphous atorvastatin (9 g) and crystalline Form I atorvastatin (1 g) are stirred at about 40°C in  
15 a mixture of water (170 mL) and methanol (30 mL) for a total of 17 hours. The mixture is filtered, rinsed with water, and dried at 70°C under reduced pressure to give crystalline Form I atorvastatin (9.7 g).

#### 20 EXAMPLE 2

[R-(R\*,R\*)]-2-(4-fluorophenyl)- $\beta$ , $\delta$ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form II Atorvastatin)

25 A mixture of amorphous and crystalline Form I atorvastatin (100 g) was suspended in a mixture of methanol (1200 mL) and water (800 mL) and stirred for 3 days. The material was filtered, dried at 70°C under reduced pressure to give crystalline Form II  
30 atorvastatin.

-28-

## EXAMPLE 3

[R-(R\*,R\*)]-2-(4-fluorophenyl)- $\beta$ , $\delta$ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form IV Atorvastatin)

5 A mixture of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (atorvastatin lactone) (United States Patent Number  
10 5,273,995) (12 kg), MTBE (50 kg), methanol (30 L) is reacted with an aqueous solution of sodium hydroxide (1.83 kg in 150 L) at 50-55°C for 30-45 minutes to form the ring-opened sodium salt. After cooling to 20-25°C, the organic layer is discarded and the aqueous layer is  
15 again extracted with MTBE (37 kg). The organic layer is discarded and the aqueous solution of the sodium salt is heated to 70-80°C and the residual MTBE is removed by distillation. The solution is then cooled to 60-70°C. To this solution is added a solution of  
20 calcium acetate hemihydrate (1.91 kg) dissolved in water/methanol (72 L water + 16 L methanol). The mixture is seeded with crystalline Form I atorvastatin (180 g) shortly after addition of the calcium acetate solution. The mixture is heated at 65-75°C for at  
25 least 5 minutes and then cooled to 50-55°C. The mixture is filtered and slurried in methanol (about 200 L) at 55-65°C and then cooled to 25-30°C and filtered. The solid is dried at 66-70°C under vacuum to give Form IV of crystalline atorvastatin (about 3 kg  
30 isolated).

-29-

## CLAIMS

1. Crystalline Form I atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the  $2\theta$ , d-spacings, and relative intensities with a relative intensity of >20% measured after 2 minutes of grinding using  $\text{CuK}\alpha$  radiation:

	$2\theta$	d	Relative Intensity (>20%) Ground 2 Minutes
10	9.150	9.6565	42.60
	9.470	9.3311	41.94
	10.266	8.6098	55.67
	10.560	8.3705	29.33
15	11.853	7.4601	41.74
	12.195	7.2518	24.62
	17.075	5.1887	60.12
	19.485	4.5520	73.59
	21.626	4.1059	100.00
20	21.960	4.0442	49.44
	22.748	3.9059	45.85
	23.335	3.8088	44.72
	23.734	3.7457	63.04
	24.438	3.6394	21.10
25	28.915	3.0853	23.42
	29.234	3.0524	23.36

2. Crystalline Form I atorvastatin and hydrates thereof characterized by the following solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million:

-30-

	Assignment (7 kHz)	Chemical Shift
5	C12 or C25	182.8
	C12 or C25	178.4
	C16	166.7 (broad) and 159.3
	Aromatic Carbons	
10	C2-C5, C13-C18, C19-C24, C27-C32	137.0
		134.9
		131.1
		129.5
		127.6
15		123.5
		120.9
		118.2
		113.8
	C8, C10	73.1
20		70.5
		68.1
		64.9
	Methylene Carbons	
	C6, C7, C9, C11	47.4
25		41.9
		40.2
	C33	26.4
		25.2
	C34	21.3

3. Crystalline Form I atorvastatin of Claim 1 in which the hydrate is a trihydrate.
4. Crystalline Form II atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of



-31-

the  $2\theta$ , d-spacings, and relative intensities with  
a relative intensity of >20% measured after  
2 minutes of grinding using  $\text{CuK}\alpha$  radiation:

5

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15

$2\theta$	d	Relative Intensity (>20%) Ground 2 Minutes
5.582	15.8180	42.00
7.384	11.9620	38.63
8.533	10.3534	100.00
9.040	9.7741	92.06
12.440 (broad)	7.1094	30.69
15.771 (broad)	5.6146	38.78
17.120-17.360 (broad)	5.1750-5.1040	63.66-55.11
19.490	4.5507	56.64
20.502	4.3283	67.20
22.706-23.159 (broad)	3.9129-3.8375	49.20-48.00
25.697 (broad)	3.4639	38.93
29.504	3.0250	37.86

5. Crystalline Form II atorvastatin and hydrates thereof characterized by the following solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million:

- 32 -

5	Assignment	Chemical Shift
	Spinning Side Band	209.1
	Spinning Side Band	206.8
	C12 or C25	181 (broad)
	C12 or C25	163 (broad)
10	C16	161 (broad)
	Aromatic Carbons	
	C2-C5, C13-C18, C19-C24, C27-C32	140.5
		134.8
		133.3
15		129.0
		122.9
		121.4
		120.3
		119.0
20		117.1
		115.7
		114.7
	C8, C10	70.6
		69.0
25		68.0
		67.3
	Spinning Side Band	49.4
	Spinning Side Band	48.9
	Methylene Carbons	
30	C6, C7, C9, C11	43.4
		42.3
		41.7
		40.2
	C33	27.5
35	C34	22.8 (broad)

-33-

6. Crystalline Form IV atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the  $2\theta$ , d-spacings, and relative intensities with a relative intensity of >15% measured using  $\text{CuK}\alpha$  radiation:

5

	$2\theta$	d	Relative Intensity (>15%)
	4.889	18.605	38.45
10	5.424	16.2804	20.12
	5.940	14.8660	17.29
	7.997	11.0465	100.00
	9.680	9.1295	67.31
	10.416	8.4859	20.00
15	12.355	7.1584	19.15
	17.662	5.0175	18.57
	18.367	4.8265	23.50
	19.200	4.6189	18.14
	19.569	4.5327	54.79
20	21.723	4.0879	17.99
	23.021	3.8602	28.89
	23.651	3.7587	33.39
	24.143	3.6832	17.23

7. Crystalline Form IV atorvastatin and hydrates thereof characterized by the following solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million:

-34-

	Assignment	Chemical Shift
5	C12 or C25	186.4
		184.9
	C12 or C25	181.4
		179.3
	C16	166.1 (broad) and 159.0 (broad)
10	Aromatic Carbons	
	C2-C5, C13-C18, C19-C24, C27-C32	138.1 (broad)
		134.7
		129.2
		127.1
		122.7
		119.8
		115.7
	C8, C10	71.5
		67.9
15		66.3
		63.5
	Methylene Carbons	
	C6, C7, C9, C11	46.1
		43.4
		42.1
		40.0
	C33	25.9
	C34	20.3
		19.4
		17.9

-35-

8. A pharmaceutical composition in the form of  
tablets comprising crystalline Form I atorvastatin  
as defined in Claim 1 in admixture with at least  
one pharmaceutically acceptable excipient,  
5 diluent, or carrier.
9. A pharmaceutical composition in the form of  
capsules comprising crystalline Form I  
atorvastatin as defined in Claim 1 in admixture  
with at least one inert pharmaceutically  
5 acceptable excipient, diluent, or carrier.
10. A pharmaceutical composition in the form of a  
powder comprising crystalline Form I atorvastatin  
as defined in Claim 1 in admixture with at least  
one inert pharmaceutically acceptable excipient,  
5 diluent, or carrier.
11. A pharmaceutical composition in the form of  
lozenges comprising crystalline Form I  
atorvastatin as defined in Claim 1 in admixture  
with at least one inert pharmaceutically  
5 acceptable excipient, diluent, or carrier.
12. A pharmaceutical composition in the form of  
suppositories comprising crystalline Form I  
atorvastatin as defined in Claim 1 in admixture  
with at least one inert pharmaceutically  
5 acceptable excipient, diluent, or carrier.
13. A pharmaceutical composition in the form of  
retention enemas comprising crystalline Form I  
atorvastatin as defined in Claim 1 in admixture  
with at least one inert pharmaceutically  
5 acceptable excipient, diluent, or carrier.

-36-

14. A method of treating hyperlipidemia and hypercholesterolemia comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
15. A process for the preparation of crystalline Form I atorvastatin comprising:  
Step (a) treating an aqueous solution of a basic salt of [R-(R\*,R\*)]-2-(4-fluorophenyl)- $\beta$ , $\delta$ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid with a calcium salt; and  
Step (b) isolating crystalline Form I atorvastatin.
16. A process according to Claim 15 wherein in Step (a) seeds of crystalline Form I atorvastatin are added during or after treating the aqueous solution of a basic salt of [R-(R\*,R\*)]-2-(4-fluorophenyl)- $\beta$ , $\delta$ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid with a calcium salt.
17. A process according to Claim 15 wherein in Step (a) the aqueous solution contains a hydroxylic co-solvent and methyl tert-butyl ether.
18. A process according to Claim 17 wherein in Step (a) the hydroxylic co-solvent is methanol.
19. A process according to Claim 15 wherein in Step (a) the calcium salt is calcium acetate.

-37-

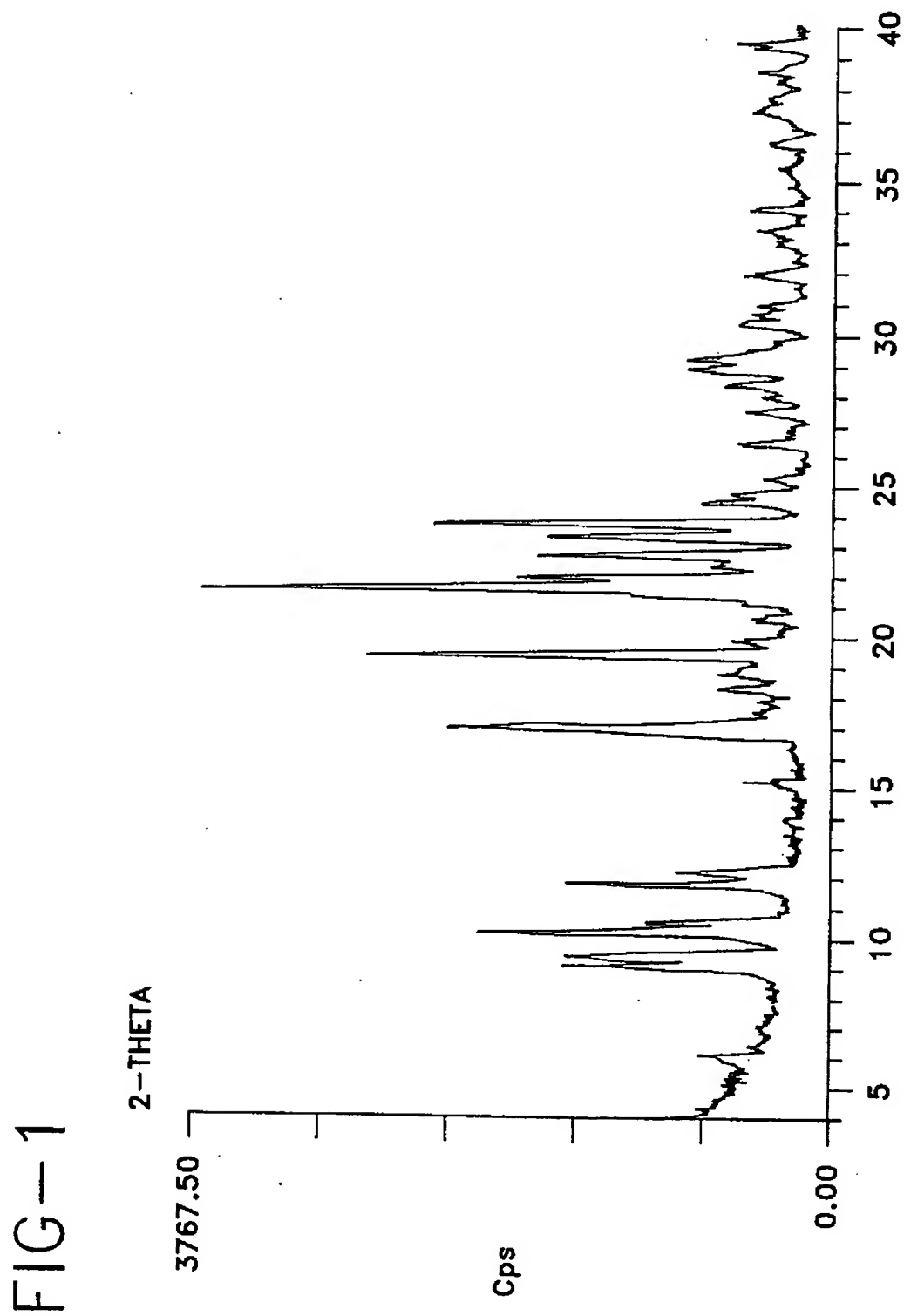
20. A process according to Claim 15 wherein in Step (b) crystalline Form I atorvastatin is further dried.
21. A process according to Claim 20 wherein in Step (b) crystalline Form I atorvastatin is further dried under reduced pressure.
22. A process according to Claim 15 wherein in Step (a) the basic salt is selected from the group consisting of an alkali metal salt, ammonia, and an amine salt.
23. A process according to Claim 22 wherein in Step (a) the basic salt is the sodium salt.
24. A process according to Claim 15 wherein two moles of the basic salt to one mole of the calcium salt is used.
25. A process for the preparation of crystalline Form I atorvastatin comprising:  
Step (a) suspending a mixture of amorphous atorvastatin and crystalline Form I atorvastatin  
5 in water containing a co-solvent; and  
Step (b) isolating crystalline Form I atorvastatin.
26. A process according to Claim 25 wherein in Step (a) the co-solvent is selected from the group consisting of methanol, ethanol, 2-propanol, and acetone.
27. A process according to Claim 26 wherein in Step (a) the co-solvent is methanol.

-38-

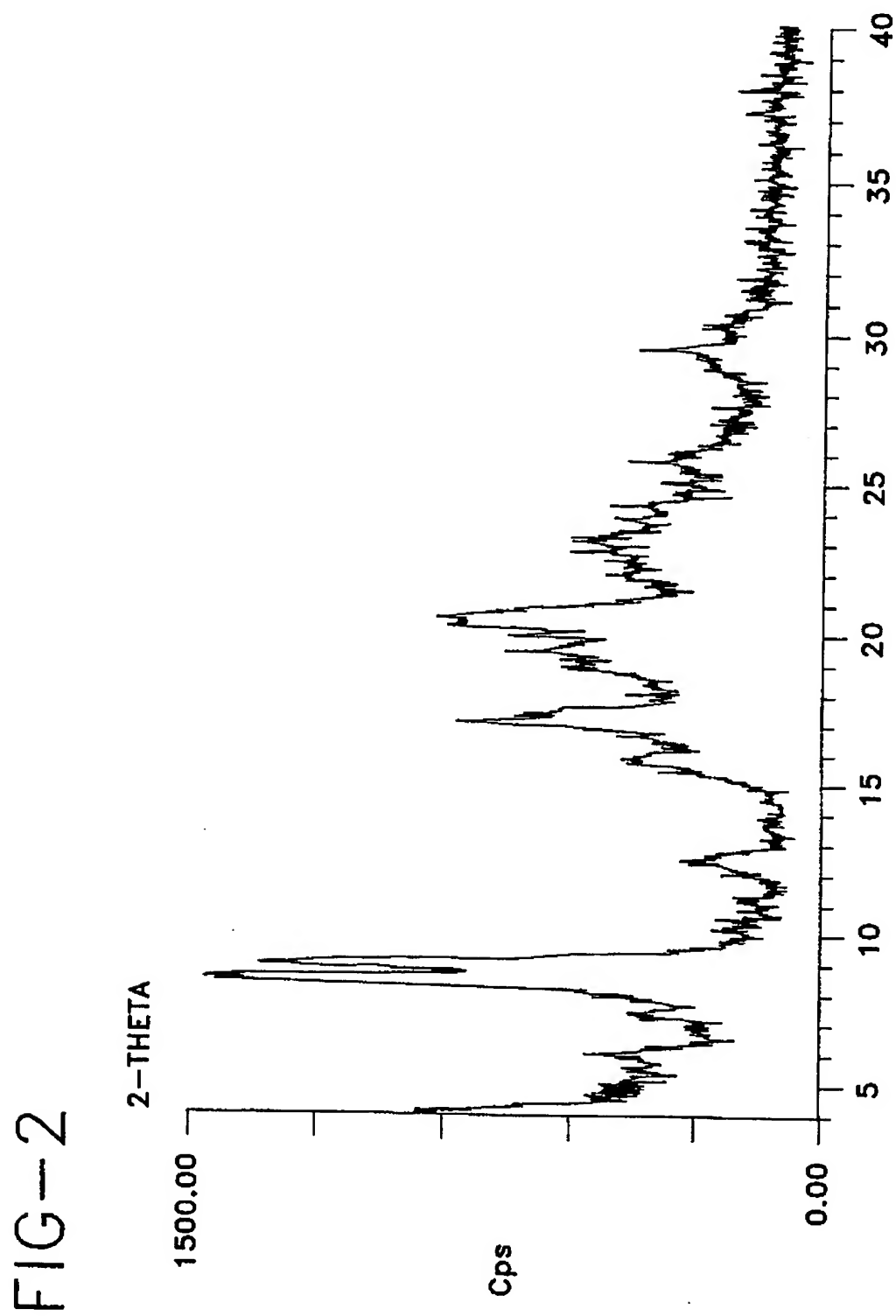
28. A process according to Claim 25 wherein in Step (b) crystalline Form I atorvastatin is further dried.
29. A process according to Claim 28 wherein in Step (b) crystalline Form I atorvastatin is further dried under reduced pressure.



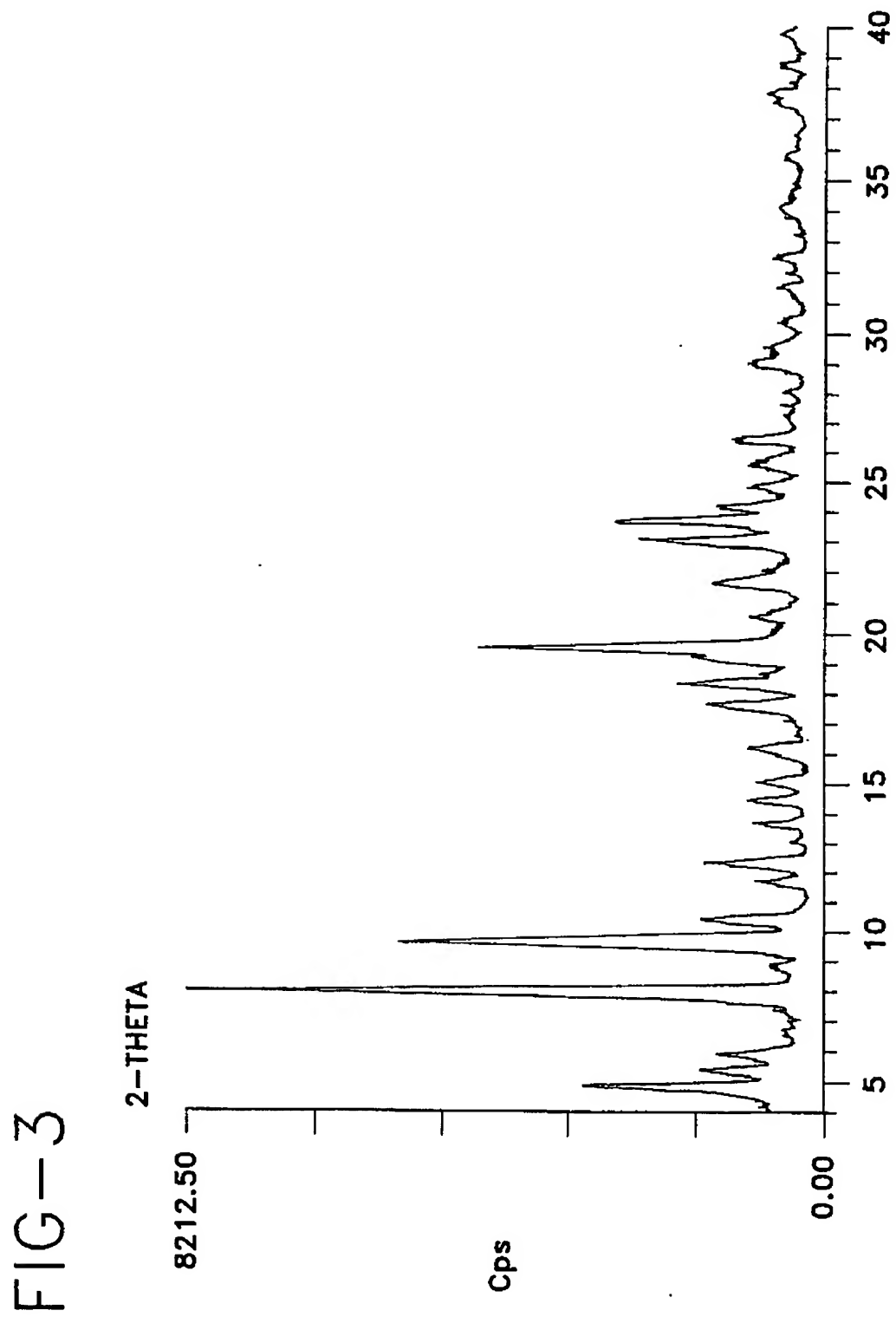
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2/6

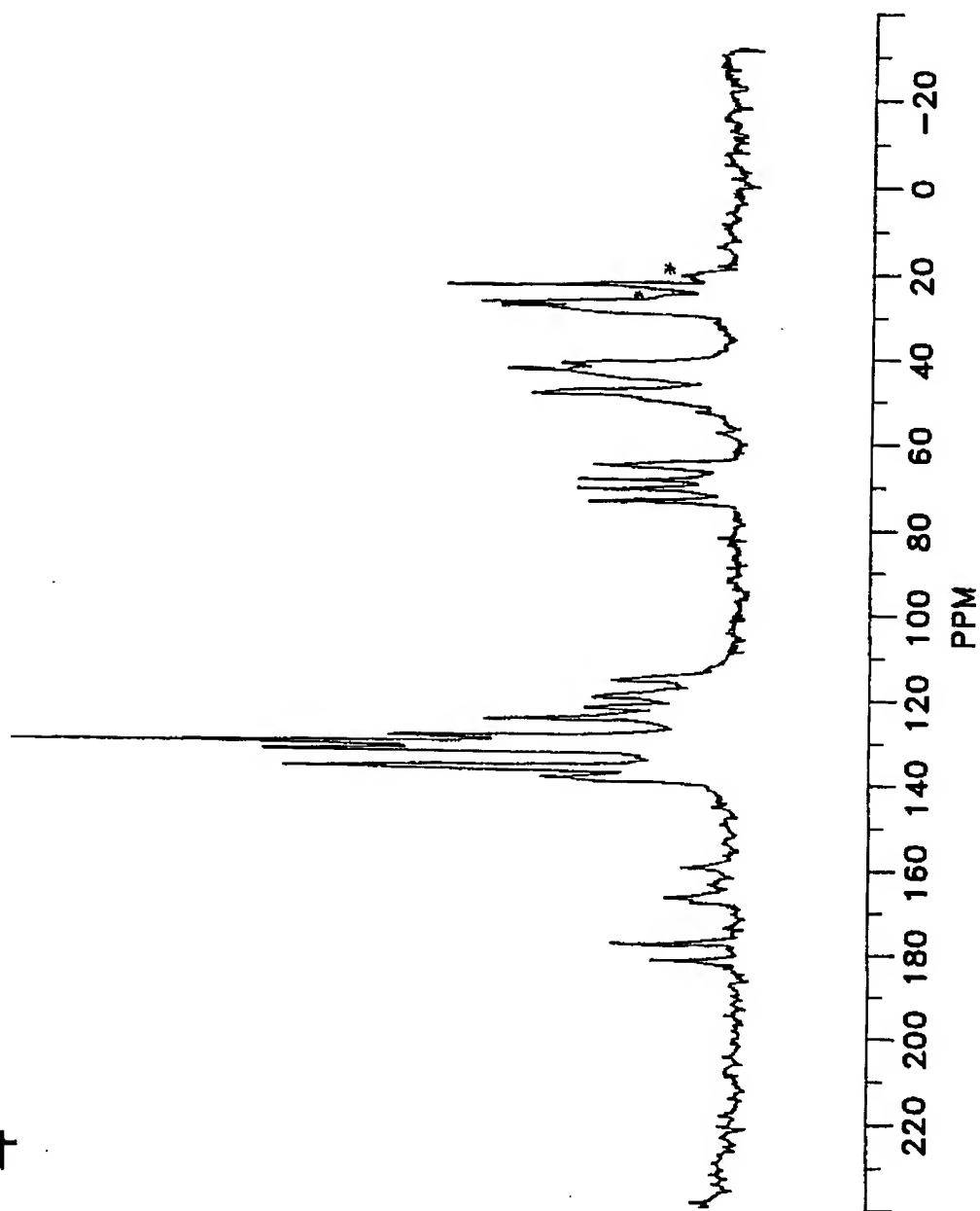


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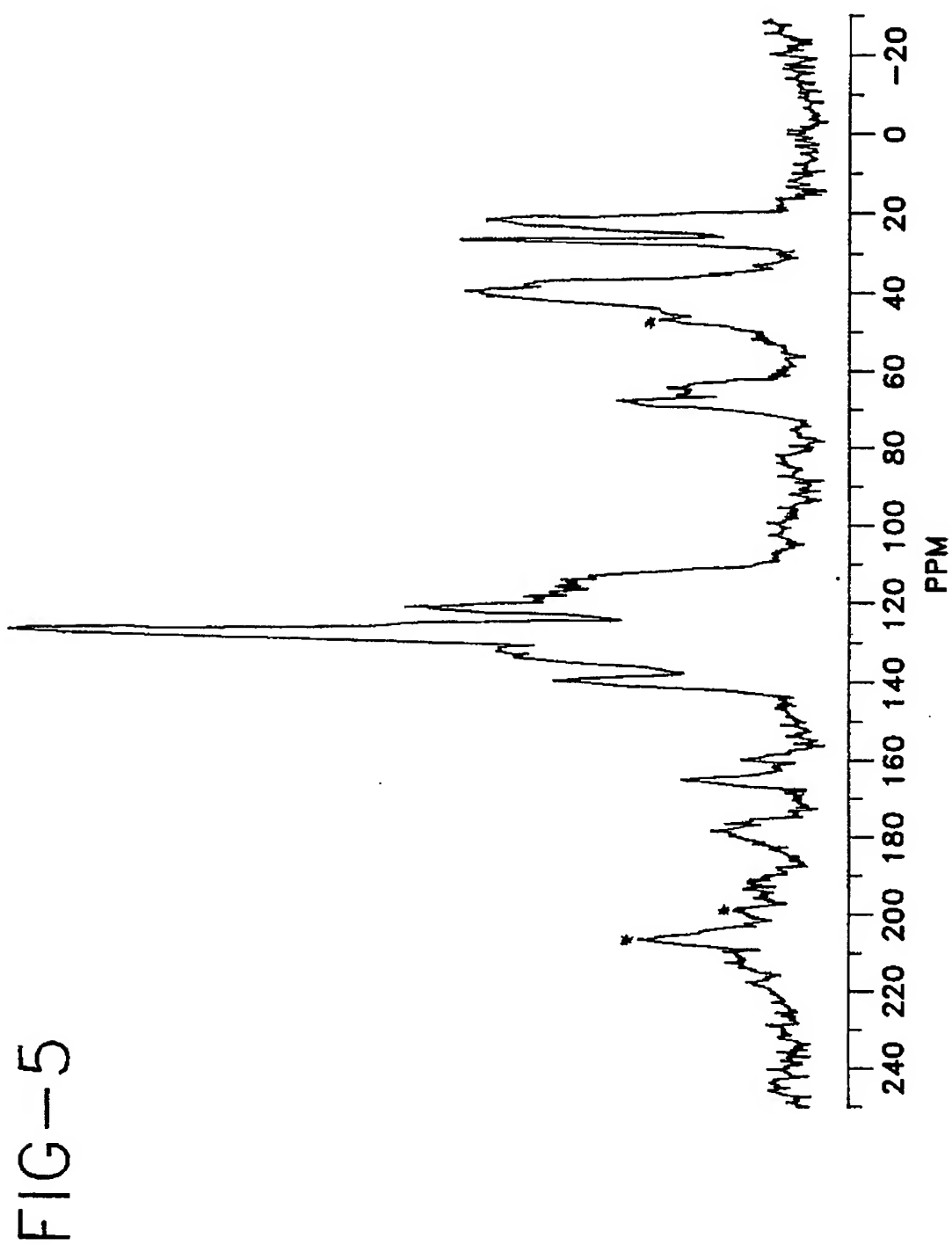


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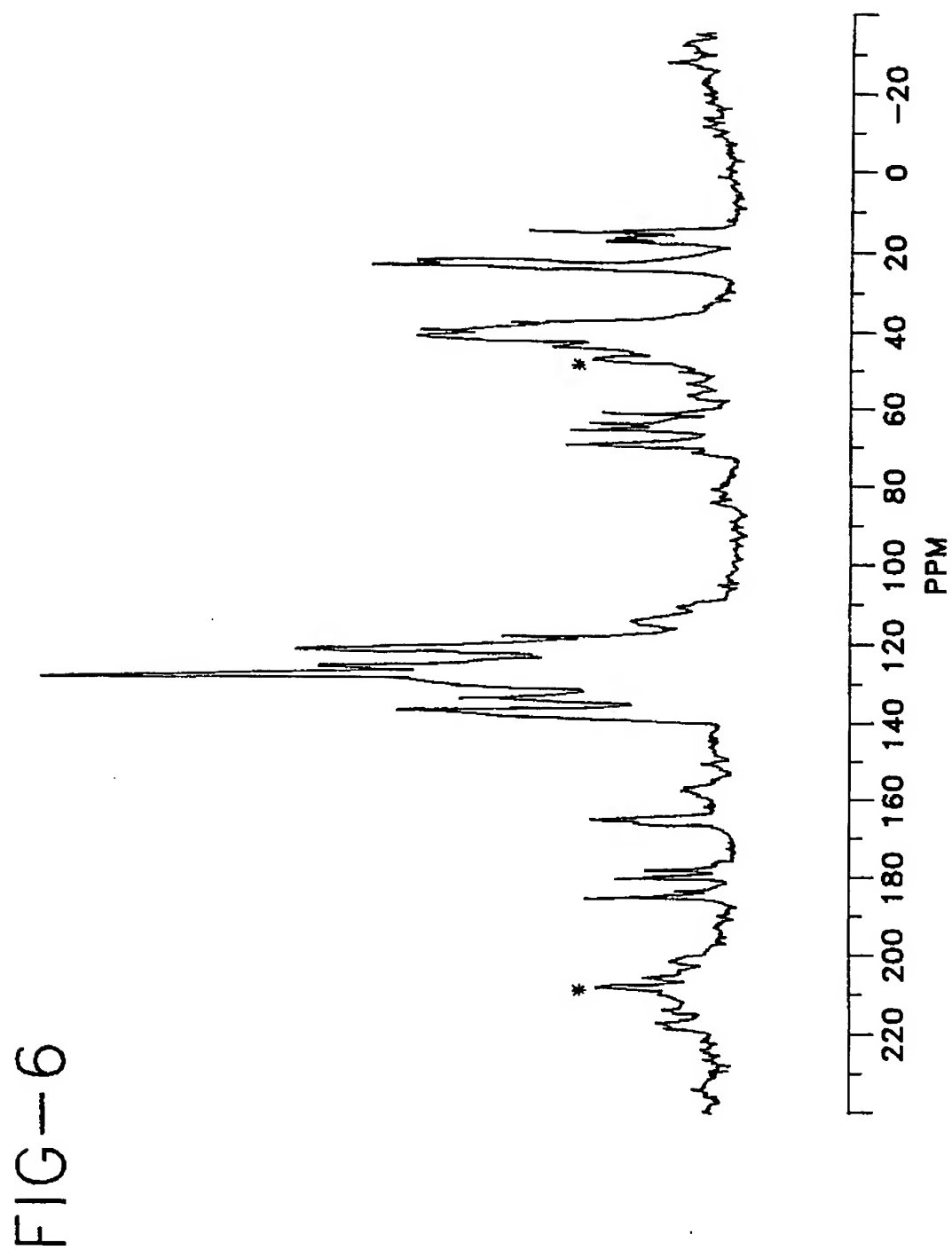
FIG-4



5/6



6/6



## INTERNATIONAL SEARCH REPORT

International Application No.

PC1/US 96/11368

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07D207/34 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 16693 A (WARNER-LAMBERT CO., USA) 4 August 1994 see the whole document ---	1-29
A	US 5 316 765 A (FOLKERS, KARL A. ET AL) 31 May 1994 see the whole document ---	1-29
A	TETRAHEDRON LETT. (1992), 33(17), 2283-4 CODEN: TELEAY;ISSN: 0040-4039, 1992, XP000608147 BAUMANN, KELVIN L. ET AL: "The convergent synthesis of CI-981, an optically active, highly potent, tissue-selective inhibitor of HMG-CoA reductase" see the whole document ---	1-29
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

18 October 1996

Date of mailing of the international search report

29.10.96

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 96/11368

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 409 281 A (WARNER-LAMBERT CO., USA) 23 January 1991 see the whole document -----	1-29



## INTERNATIONAL SEARCH REPORT

national application No.

PCT/US 96/ 11368

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claim 14 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/11368

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9416693	04-08-94	CA-A- 2150372	04-08-94
		EP-A- 0680320	08-11-95
		JP-T- 8505640	18-06-96
US-A-5316765	31-05-94	US-A- 5082650	21-01-92
EP-A-0409281	23-01-91	AU-B- 628198	10-09-92
		AU-A- 5972490	24-01-91
		CA-A- 2021546	22-01-91
		FI-B- 94339	15-05-95
		JP-A- 3058967	14-03-91
		NO-B- 174709	14-03-94
		NO-B- 176096	24-10-94
		US-A- 5273995	28-12-93